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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
873-Z-US

I hereby certify that this correspondence is being facsimile-transmitted to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 [37 CFR 1.8(a)]

on April 16, 2007

Signature Albert Wai Kit Chan

Typed or printed name Albert Wai-Kit Chan

Application Number	Filed
10/738,423	December 16, 2003
First Named Inventor	
Ivan C. KING	
Art Unit	**Examiner**
1633	Qian Janice Li

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 36,479
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Albert Wai Kit Chan
Signature

Albert Wai-Kit Chan
Typed or printed name

718-799-1000
Telephone number

April 16, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of 1 forms are submitted.

Dkt. 873-Z-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: King, et al.,
U.S. Serial No.	: 10/738,423
Confirmation No.	: 8783
Filed	: December 16, 2003
Art Unit	: 1633
Examiner	: Qian Janice Li
For	: COMPOSITIONS AND METHODS FOR TUMORTARGETED DELIVERY OF EFFECTOR MOLECULES

Law Offices of Albert WaiKit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, NY 11357

April 16, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES AND PRE-APPEAL BRIEF REQUEST FOR REVIEW

The Notice of Appeal from the Examiner to the Board of Patent Appeals and Interferences (**Exhibit A**, 1 page) and the Pre-Appeal Brief Request for Review (**Exhibit B**, 1 page) are being submitted in response to the Final Office Action dated December 14, 2006 and the Advisory Action of April 5, 2007. A period for reply is set to expire 4 months from the mailing date of the Final Office Action, i.e., by April 14, 2007. Since April 14, 2007 is a Saturday, the deadline is moved to the next business day, i.e. April 16, 2007. Accordingly, this Request is herewith timely filed.

I. Background

Applicant respectfully requests that the following comments be considered for the purposes of;
reversing the rejections under (1) 35 U.S.C. § 112, 2nd paragraph and (2) 35 U.S.C. § 103(a) over Low et al., (Nature Biotechnology 1999, 17:37-41) in view of Schachter et al., (Cancer Biother Radiopharm 1988, 13:155-164).

II. Pending Claims

Claims 100, 103, 106, 108 and 111-112 are pending in this application. No claims are deemed allowable. In order to avoid exceeding the five page limit for this request a copy of the claims has not been attached. However, a copy of the pending claims may be found in the response and amendment filed on March 29, 2007.

III. **The Language of the Pending Claims is Not Indefinite**

On page 4 of the Final Office Action it is asserted that,

> [t]he claims are vague and indefinite because of the claim limitation, "attenuated tumor-targeting" bacteria. The specification fails to define ***what structure is required*** for a bacterium to possess that would meet claim limitation, particularly for the term "tumor-targeting", and thus the metes and bounds of the claims are unclear. (Emphasis added).

Applicants respectfully disagree that the claims are vague and indefinite. Further, Applicants respectfully submit that Examiner's rationale is not even a proper basis for alleging indefiniteness.

A. The legal standard under § 112,2nd paragraph

The definiteness of claim language must be analyzed, not in a vacuum, but in light of:
(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. MPEP 2173.02.

It is respectfully submitted that Examiner's comments in the Final Office Action do not address the understanding of persons of ordinary skill in the art or the teaching of the specification

Attention is respectfully directed to each of the last paragraphs on pages 20 and 22 of the specification, wherein the definitions of *attenuated* and *tumor-targeting*, respectively, are provided. Persons of ordinary skill in the art would undoubtedly appreciate these relevant attributes that comprise attenuated bacteria that preferentially localize in tumors. It is respectfully submitted that this is all that is required to satisfy the definiteness requirement of § 112, 2nd paragraph.

Examiner's interpretation of the relevant part of the specification states:

> Page 22 of the specification reads, "tumor-targeted is defined as the ability to preferentially localize to a cancerous target cell or tissue relative to a non-cancerous counterpart cell or tissue and replicate". This passage does ***not make clear what structure*** would make a bacteria having the ability of tumor-targeting. Thus, it is still unclear what bacteria the claims encompass. (Emphasis added here).

However, the claims are not directed to a "structure" for tumor-targeting, but a bacterium that clearly fulfills the expectations of those of ordinary skill in the art. Respectfully, Examiner seems to be imposing her own standard of definiteness on the claims, wherein she requires an understanding of the mechanism of how the invention operates rather than the standard set out in the statute and by the courts

B. The Final Office Action Relies on Unsound Scientific Theory

When an Examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided. MPEP 2144.02, *citing In re Grose*, 137 USPQ 797 (CCPA 1963).

In the present case, Examiner makes a substantial assumption that is completely unsupported by any theory or evidence in the microbiological arts. Specifically Examiner assumes that the basis of the tumor-targeting phenotype can be reduced to a single, unitary "structure." There is no data on record or in the art to even suggest that this is the case. Therefore, basing the rejection on this unsound

scientific "hypothesis" is improper and is insufficient to set forth a *prima facie* case of vague and indefinite claim language.

Further, the requirements for clarity and precision must be balanced with the limitations of the language and the science. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the statute (35 U.S.C. 112, second paragraph) demands no more. MPEP 2175.03 (Emphasis added).

C. "Toxic lipopolysaccharide (LPS)" is not Vague or Indefinite

Examiner asserts that "the amended claims recite "toxic LPS", and it is unclear what is the structure of the toxic LPS, and thus the metes and bounds of the claims are uncertain." Applicants respectfully submit that this rejection is improper and should be reversed.

Attention is respectfully directed to U.S. Patent Publication 20040229338, paragraphs [0152]-[0153]. These paragraphs describe that LPS is one of the bacterial substituents responsible for toxicity of bacteria. The text further indicates that persons of ordinary skill in the art may produce better tolerated bacteria, i.e., attenuated, by producing bacteria lacking toxic LPS. One way of achieving this is disruption of Lipid A synthesis.

Paragraphs [0152]-[0153] succinctly explain why it is indisputable that persons of ordinary skill in the art would have no problems appreciating that an attenuated bacterium that cannot produce toxic LPS will demonstrate an attenuated phenotype.

Applicants respectfully submit that the claim language would not be indefinite or vague to persons of ordinary skill in the art. As discussed above, Examiner substitutes her own state of knowledge for those of ordinary skill in the art in order to maintain the rejections under § 112, 2nd paragraph.

In sum, the rejection of the claims under § 112, 2nd paragraph should be reversed. The rationale for the rejections is improper as it is not directed not toward understanding claim language, but requiring a nonexistent explanation of the invention's operability. Specifically, Examiner believes that a single structure confers the tumor-targeting phenotype and that it must be reflected in the claim. Similarly, Examiner's comments about the structure of "toxic LPS," are improper in view of the specification's explicit disclosure and knowledge of persons of ordinary skill in the art. Accordingly, reversal of the rejection is respectfully requested.

IV. The Claimed Subject Matter is not Obvious Over the Combination of Low in View of Schachter

The pending claims are drawn to a method of inhibiting the growth or reducing the volume of a solid tumor by administering attenuated tumor-targeted bacteria and either cisplatin or cytoxan. In contrast, Schachter teaches using four distinct drugs (one of which is cisplatin) after treatment with IFN-α but before treatment with GM-CSF. Schachter, page 156, top col. 1, discussing the Del Prete reference. No tumor-targeting bacteria are disclosed.

On page 6 of the Final Office Action, Examiner asserts:

> The Office cited Schachter et al to show the need and motivation was present in the art to combine chemotherapy with bio-therapy, one could use either the cytokine biotherapy as taught

by *Schachter et al*, or the attenuated *Salmonella* biotherapy as taught by *Low of* al with a reasonable expectation of success for treating cancer. It was within the levels of the skilled in the art, and a matter of optimization to determine the proper dosing regimen so that the combined therapy would not lead to a detrimental effect.

Applicants respectfully disagree that a mere general reference to a "need and motivation" in the art, cannot provide a reasonable expectation of success. Further, said conclusion runs counter to current practice in the art. Accordingly, the combination of Low and Schachter does not provide a *prima facie* case of obviousness.

1. Proceeding contrary to accepted wisdom is evidence of nonobviousness. MPEP 2145(X.D.3). In contrast to Examiner's conclusion it is respectfully submitted that Appellants' use of tumor-targeted bacteria in a combination chemotherapy regimen goes against commonly accepted thinking in the chemotherapy arts. It is known that chemotherapy often results in a severe decrease of neutrophils, a condition known as neutropenia. A major result is a severely compromised ability of the cancer patient to fight infection against bacterial and fungal pathogens. *See* Freifeld, et al., (2004), *Fever in the Neutropenic Cancer Patient*, Chap. 46, Clinical Oncology, (3rd ed.). It is known that when unopposed by innate neutrophil responses bacterial infections spread quickly and relentlessly.

Therefore, in contrast to Examiner's conclusion persons of ordinary skill in the art would be highly unlikely to employ Low's tumor-targeted bacteria in a chemotherapy regimen similar to that of Schachter. Accordingly, the combination of Low and Schachter are not sufficient to establish a *prima facie* case of obviousness and, therefore, the rejection should be reversed.

2. Examiner concludes, without any scientific explanation, that Low's tumor-targeted bacteria and Schacter's biotherapy regimen of two cytokines, IFN-α and GS-CSF, are freely interchangeable Further, Low does not teach any combination therapy at all. Thus, the prior art does not provide any motivation or suggestion to combine the bacteria with only cisplatin or cytoxan. Examiner's rationale is nothing more than an obvious-to-try suggestion, which is not sufficient to make out a *prima facie* case of obviousness. In re Eli Lilly and Co., 14 USPQ 2d 1741, 1743 (Fed. Cir. 1990))(An "obvious to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.)

3. The rationale behind In re Kerkhoven is incorrectly applied in this case for two reasons. First, the technical subject in Kerkhoven is far more predictable than that in the present case. For example, in Kerkhoven mixing two detergent compositions to form a third effective detergent composition has a substantial expectation of success. This is known not to be the case with developing effective combination cancer therapies. The Office Action asserts that "one could use either the cytokine biotherapy as taught by Schachter et al, or the attenuated Salmonella biotherapy as taught by Low et al with a reasonable expectation of success for treating cancer." A major problem with this conclusion is that it does not take into consideration the unpredictability of effectiveness of combinations of chemotherapy agents.

Second, Examiner has not provide a single piece of evidence that tumor-targeted bacteria are ***art-recognized equivalents*** of IFN-α and/or GM-CSF. See MPEP 2144.06. Examiner loosely associates them under the umbrella of "biotherapy" in order to support her rationale. Respectfully, doing so has no art-recognized basis or any legal effect in establishing that they are art-recognized equivalents. Accordingly, it is respectfully requested that the rejection be reversed.

4. A comparison of the claimed method with the closest prior art available (i.e., Fig. 40) proves that the Examiner's allegation of a "reasonable expectation of success" is unfounded. Attention is respectfully directed to Figs 39 and 41, which show the supra-additive effect of the combination of bacteria and either cytoxan or cisplatin, respectively. In contrast, Fig. 40 demonstrates that the combination of mitomycin with the same bacteria provide no extra benefit over that provided by the bacteria themselves. Therefore, changing even one therapeutic agent may obliterate the supra-additive effect of the claimed method.

In view of this data, it cannot be reasonably concluded that combining Low and Schachter provides a reasonable expectation of success sufficient to make out a *prima facie* case of obviousness. Accordingly, the rejection should bereversed.

V. Conclusion

In sum, the rejection of the claims over Low/Schachter should be reversed. Examiner's proposed modification of Low is clearly contrary to current chemotherapy practice. Further, the remarks and experimental data show that persons of ordinary skill in the art could not have had a reasonable expectation of success of combining the cited references and arriving at the claimed method. Further, Examiner's invoking the rule of Kerkhoven is misplaced and cannot support the instant rejection. Accordingly, the rejection under
§ 103(a) should be reversed.

Respectfully submitted,

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Exhibit A

Exhibit B